

HSV-sr39TK positron emission tomography and suicide gene elimination of human hematopoietic stem cells and their progeny in humanized mice.

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Public Summary:

The realized potency of engineered immunotherapy has resulted in a flood of experimental treatments to the clinic. Redirecting cells of the immune system to kill solid cancers and leukemias using cancer-targeting receptors has shown efficacy, and indeed cure, for previously intractable disease. In our study we sought to investigate the use of human hematopoietic (blood) stem cells (HSCs) for cancer immunotherapy. We modified human HSCs using a virus that encodes a T cell receptor against the cancer antigen NY-ESO-1 as well as a dual-purpose imaging / suicide gene, then transplanted them into immunocompromised mice to study their development. We found that HSCs gave rise to T cells that targeted and killed NY-ESO-1 expressing cancer cells, providing support for the use of stem cells in engineered immunotherapy. Using positron emission tomography we were able to visualize all of the gene-modified cells in the body, and found they were abundant in marrow spaces, and importantly the thymus: the organ that supports immune cell development and maturation. Finally, we showed the selective destruction of engineered cells by giving the mice a drug injection, demonstrating the ability to safely control these cells and remove them from the body if necessary. Our work supports the use of stem cells for cancer immunotherapy in humans, and represents a step towards the clinic for gene therapy for cancer.

Scientific Abstract:

Engineering immunity against cancer by the adoptive transfer of hematopoietic stem cells (HSC) modified to express antigen-specific T-cell-receptors (TCR) or chimeric antigen receptors (CAR) generates a continual supply of effector T-cells, potentially providing superior anti-cancer efficacy compared with the infusion of terminally differentiated T-cells. Here we demonstrate the in vivo generation of functional effector T-cells from CD34-enriched human peripheral blood stem cells (PBSC) modified with a lentiviral vector designed for clinical use encoding a TCR recognizing the cancer/testes antigen NY-ESO-1, co-expressing the PET /suicide gene sr39TK. Ex vivo analysis of T-cells showed antigen- and HLA-restricted effector function against melanoma. Robust engraftment of gene-modified human cells was demonstrated with PET reporter imaging in hematopoietic niches such as femurs, humeri, vertebrae, and the thymus. Safety was demonstrated by the in vivo ablation of PET signal, NY-ESO-1-TCR bearing cells, and integrated lentiviral vector genomes upon treatment with ganciclovir (GCV), but not with vehicle control. Our study provides support for the efficacy and safety of gene-modified HSCs as a therapeutic modality for engineered cancer immunotherapy.

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